1: Dis Markers 1991 May-Aug;9(3-4):225-31 Related Articles, Links

Antibody directed enzyme prodrug therapy (ADEPT): a three phase system.

Sharma SK, Bagshawe KD, Springer CJ, Burke PJ, Rogers GT, Boden JA, Antoniw P, Melton RG, Sherwood RF.

Department of Medical Oncology, Charing Cross Hospital, London, U.K.

Monoclonal anti-CEA antibody, A5B7, and its fragments conjugated to CPG2 localize to a peak concentration in the LS174T xenografts within 24 h after injection, but enzyme activity persists in plasma such that prodrug injection has to be delayed for 5-6 days in order to avoid toxicity. Injection of prodrug at this time did not result in growth delay of this tumour. A three-phase system has been developed in which residual plasma enzyme was inactivated and cleared by a galactosylated anti-CPG2 antibody, SB43gal, allowing prodrug administration within 24 h after the conjugate. Using this three-phase system, a marked growth delay of this tumour was achieved after a single course of treatment consisting of conjugate injection followed by SB43gal, 19 h later and three doses of the prodrug.

PMID: 1813212 [PubMed - indexed for MEDLINE]

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1: Biochem Soc Trans 1990 Oct;18(5):750-2

Antibody-directed enzyme/prodrug therapy (ADEPT).

Bagshawe KD.

Department of Medical Oncology, Charing Cross Hospital, London, U.K.

Publication Types:
- Review
- Review, Tutorial

PMID: 2083666 [PubMed - indexed for MEDLINE]

☐ 1: Eur J Cancer 1991;27(11):1361-6 Related Articles, Links

Ablation of human choriocarcinoma xenografts in nude mice by antibody-directed enzyme prodrug therapy (ADEPT) with three novel compounds.

Springer CJ, Bagshawe KD, Sharma SK, Searle F, Boden JA, Antoniw P, Burke PJ, Rogers GT, Sherwood RF, Melton RG.

Department of Medical Oncology, Charing Cross Hospital, London, U.K.

Three novel prodrugs have been designed for use as anticancer agents. Each is a bifunctional alkylating agent which has been protected to form a relatively inactive prodrug. They are designed to be activated to their corresponding alkylating agents at a tumour site by prior administration of an antitumour antibody conjugated to the bacterial enzyme carboxypeptidase G2 (CPG2) in a two-phase system called antibody-directed enzyme prodrug therapy (ADEPT). The Km and Vmax values for three different antibody-CPG2 conjugates were determined in relation to each prodrug. The Km values ranged from 4.5-12 mumol/l and the Vmax from 0.5-1.6 mumol/U/min. Athymic Nu/Nu mice with palpable transplanted human choriocarcinoma xenografts, which are resistant to conventional chemotherapy, were treated with anti-human chorionic gonadotropin antibodies conjugated to CPG2. This was followed by each of the three novel prodrugs. Significant increase in survival was obtained in three of the regimens tested using only one course of treatment. This demonstrates the potential of a tumour-localised bacterial enzyme to activate protected alkylating agents in order to eradicate an established human xenograft.

PMID: 1835849 [PubMed - indexed for MEDLINE]

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1: FASEB J 1990 Feb 1;4(2):188-93 Related Articles, Links

Activation of prodrugs by antibody-enzyme conjugates: a new approach to cancer therapy.

Senter PD.

Oncogen, Seattle, Washington 98121.

A new strategy for the delivery of cytotoxic agents to solid tumors is described in which monoclonal antibodies are used as carriers for enzymes to tumor cell surfaces. The enzymes are chosen for their abilities to convert relatively noncytotoxic drug precursors (pro-drugs) into active anticancer drugs. The drugs thus formed can then penetrate into nearby tumor cells, resulting in cell death. A number of prodrugs have been developed that can be transformed into active anti-cancer drugs by enzymes of both mammalian and non-mammalian origin. The enzymes have been shown to localize into tumors when linked to monoclonal antibodies that bind to tumor-associated antigens. In vivo studies indicate that MAb-enzyme/prodrug combinations can result in antitumor activities significantly greater than those of the prodrugs or drugs given alone. This is most likely due to the generation of large amounts of active drug at the tumor site.

Publication Types:
- Review
- Review, Tutorial

PMID: 2404820 [PubMed - indexed for MEDLINE]

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☐ **1:** Br J Cancer 1987 Nov;56(5):531-2 Related Articles, Links

Antibody directed enzymes revive anti-cancer prodrugs concept.

Bagshawe KD.

Department of Medical Oncology, Charing Cross Hospital, London, UK.

PMID: 3426915 [PubMed - indexed for MEDLINE]

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1: Br J Cancer 1988 Dec;58(6):700-3

A cytotoxic agent can be generated selectively at cancer sites.

Bagshawe KD, Springer CJ, Searle F, Antoniw P, Sharma SK, Melton RG, Sherwood RF.

Department of Medical Oncology, Charing Cross Hospital, London, UK.

Attempts to improve the selectivity of anti-cancer agents by conjugating them to antibodies directed at tumour associated antigens have demonstrated tumour localisation but only limited therapeutic success. We report here the advantage of a 2-stage approach in which the first component combines the selective delivery of antibody with a capability to generate a cytotoxic agent from a second subsequently administered component. A bacterial enzyme, carboxypeptidase G2 (CPG2) was conjugated with F(ab')2 fragment of a monoclonal antibody directed at beta subunit of human chorionic gonadotrophin (beta-hCG) and injected into nude mice bearing hCG producing CC3 xenografts of human choriocarcinoma. Time was allowed for the conjugate to localise at tumour sites and clear from blood before injecting para-N-bis (2-chloroethyl) aminobenzoylglutamic acid. Cleavage of the glutamic acid moiety from this molecule by CPG2 released a benzoic acid mustard. Growth of the tumour which is resistant to conventional chemotherapy was markedly depressed by a single course of treatment. This demonstrates for the first time the potential of an antibody directed enzyme to activate an alkylating agent and to eradicate an established human cancer xenograft.

PMID: 3265633 [PubMed - indexed for MEDLINE]